LONGTERM FOLLOW-UP OF PATIENTS IN CSP #298 "TREATMENT OF PATIENTS WITH ACQUIRED DEFICIENCY SYNDROME (AIDS) AND AIDS RELATED COMPLEX"

ANNUAL REPORT

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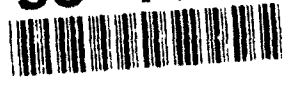

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FOREWORD

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M. S. Simberkoff by DRS.

Principal Investigator's Signature Date

I. Introduction

This is the second annual report for the extended follow-up of patients originally enrolled in the VA CSP Study No. 298. The original study was a 4-year, double-blind, placebo-controlled study of the efficacy and safety of azidothymidine (AZT: 250 mg q 4 hr, p.o.) for patients with symptomatic HIV infection and CD4 counts between 200 and 500 cells/mm^3. In that study we compared the benefits and liabilities of initiating AZT early (i.e., at study enrollment) versus initiating it late (i.e., when AIDS occurred or CD4 counts declined to < 200 cells/mm^3). That study ended in January 1991, finding that early AZT therapy delays the progression to AIDS but does not give a concomitant increase in survival time [1].

The present study is a 3-year extended follow-up of the patients who survived the original study. Its goals are to assess early versus late AZT therapy in terms of long-term morbidity, toxicity, and drug resistance. For this study, the dosage of AZT is 500 mg daily, the dosage now recommended by the manufacturer and the FDA.

II. Study results

The results reported here are based on data collected as of January 1, 1993. More than 70% of the 295 patients who were alive at the end of Part I of the study agreed to participate in Part II. The other 30% are being followed passively through the patient treatment file, which is a national database of hospital admissions to all VAs, through the death benefit registry, and through chart reviews. By these efforts we believe that we will know about most of the progressions and deaths that occur in our study population.

For the patients in this extended follow-up, most of them (90%) are, or have been, taking AZT. Some 22% have also, or instead, taken some other anti-retroviral agent such as ddI or ddC. Ten percent are, or have been, enrolled in other studies. A few have refused any anti-retroviral.

CD4 count. We now have a great deal of information about CD4 count over time. Figure 1 shows that early therapy produces an initial increase in CD4 count that is maintained over time compared with late therapy. Figure 2 shows that Blacks and Hispanics, as compared with non-Hispanic Whites, continue to appear to respond differently to the disease and/or the therapy.

Progression to AIDS. In the present extended follow-up (Part II), 42 additional patients have progressed to AIDS, 22 of whom were originally assigned to early therapy and 20 to later therapy. Combining these with those who progressed in Part I, we have a total of 118 patients who have progressed: 50 in the early-therapy group and 68 in the late-therapy group. Table 1 shows the progressions that have occurred during the entire study (Part I and II) and the breakdown according to the following patient characteristics

at entry to the study: CD4 strata (low stratum being counts between 200 and 299; high stratum being counts between 300 and 500), race, intravenous drug use, and immune status as measured by skin response to a panel of standard antigens. The early-therapy group continues to have an advantage, although over time it is diminishing and the difference between groups is no longer significant ($p = 0.07$) In the various subgroups, the relationships are much the same as they were at the end of Part I, but with the increased numbers of events more of these are now significant. The relative risks (shown as late/early therapy) remain substantially the same as they were at the end of Part I. The confidence intervals, however, are shorter.

Table 2 shows the first AIDS-defining event for those who progressed (the data is cumulative, from the beginning of Part I to the present). Of note, there are significantly fewer patients in the early-therapy group whose first event was either lymphoma ($p = 0.05$) or dementia ($p = 0.01$). Table 2 also shows the number of patients who have had subsequent AIDS-defining diagnoses. A higher proportion of patients in the early-therapy group have had an additional AIDS diagnosis compared with those in the late-therapy group (61% vs. 49%).

We are currently using the 1987 CDC definition of AIDS and plan to continue to do so. As the definition of progression to AIDS continues to broaden, however, we may at some point need to have two parallel definitions, going back over our records and reclassifying some of the patients. For us to do this, the CDC's recent inclusion of the fall in CD4 count to less than 200 would not present a problem because we have this data, but some of the other recent inclusions may prove difficult to establish with certainty in a retrospective chart review.

Survival. As of this report, approximately a third of our patients have died. In Part II, 67 patients have died: 30 in the early-therapy group and 37 in the late-therapy group. Combining these deaths with those of Part I, we have 110 deaths overall: 53 in the early-therapy group and 57 in the late-therapy group. As shown in Table 3, the overall survival continues to be the same for each treatment group. Among subgroups, however, survival remains similar to that found at the end of Part I, where Blacks and Hispanics originally assigned to placebo had fewer deaths than the Blacks and Hispanics who received AZT at study entry (early therapy).

Figure 3 shows survival after the first AIDS-defining event. Currently, the median post-AIDS survival is 16.6 months for the late-therapy patients and 11.8 months for the early-therapy patients.

We are in the process of classifying the deaths as AIDS-related and -unrelated. For the deaths that have been classified thus far, there is no difference between the two treatments (see Figure 4).

Viral resistance. To date, peripheral blood mononuclear cells from all patients who signed up for Part II, as well as the virus, if any, that is recovered from these cells, have been shipped to CDR Douglas Mayers at the Walter Reed Army Institute of Research.

Another group of specimens is currently being prepared for shipment.

Our manuscript on the case-control study of virus resistance in collaboration with Burroughs Wellcome has been accepted by the *Journal of AIDS* [2]. In this study, we recovered virus from 17 pairs of patients, where each pair was matched as to CD4 count and length of exposure to AZT. In each matched pair, the case had progressed to AIDS or had a sustained fall in CD4 count to < 200, and the control had not had either of these events. We found that viral resistance to zidovudine is associated with disease progression. We also found that the syncitium-inducing phenotype is associated with disease progression, and we speculate that this latter association may be the more important.

We are also investigating the relationship between viral resistance and outcome for the two treatment groups of our study but have no results to report yet.

Quality of life. We are continuing to analyze the quality of our patients' lives. The Sickness Impact Profile (SIP), which measures the patient's sense of physical and psychosocial well-being, shows some initial improvement in both the early-therapy and late-therapy groups for the first study year, improvement in the late-therapy group for the second study year, and improvement in the late-therapy group for the fifth study year. There are, however, no statistically significant differences between treatment groups whether one looks at the overall scores or at the separate scores for the physical and psychosocial components.

We have also reproduced the Q-TWiST analysis done by Richard Gelber for the NIH's ACTG 016 data. This analysis indicates that the patients treated early have more time without symptoms or toxicity (TWiST) (2.3 months) and less overall life (1 month). We have not yet done an error analysis, but these differences do not seem very compelling. The threshold utility analysis indicates that for a greater range of utility values early therapy is better.

Neurophychological tests. At the beginning of Part II, we began administering the Trails A and Trails B tests as a way to detect early dementia so that a complete battery of neurophyshological testing could be done at an appropriate time. There seem to be some differences between the two therapy groups, although statistical tests have not yet been done and the data are difficult to interpret. We have also looked at the Folstein Mini-Mental, which we used throughout Part I. The results suggest that early therapy is better, which could be related to the greater number of patients in the later-therapy group who received a diagnosis of HIV dementia.

Immune responses. We have investigated the relationship between various immunologic parameters and outcome. Most of the parameters shown by other authors to be related to outcome are related in our data as well. We did find, in particular, that anergy and CD4 count are independent predictors of outcome (see Table 4).

III. Conclusion

The study continues to progress well. We are confident that we will be able to follow most of our patients throughout the remainder of the study and to have access to the records of most of those who, for one reason or another, are lost to routine follow-up.

During this extended follow-up, we are amassing valuable data that no one else in this country has been able to collect because of the short duration of their studies. In a recent publication, Study Cochairman Michael S. Simberkoff, M.D., et al. addressed the problems that we confronted when other similar studies were stopped [4]. We will continue to analyze our data and to prepare our analyses for publication. There continues to be international interest in our study. The Study Cochairman John Hamilton, M.D., gave an invited presentation on the results of Part I of the study at the international AIDS meeting in Amsterdam [5], the Institut Pasteur in Paris [6], and the Karolinska Institut in Stockholm [7]. He has also been invited to make a presentation at a satellite meeting of the international AIDS conference in Berlin this summer [8].

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5. Hamilton JD. Long-term studies of AZT use. Paper presented at the "State of the Art Symposium," VIII International Conference on AIDS/III STD World Congress, Amsterdam, The Netherlands, July 22, 1992.

6. Hamilton JD. Implications of early versus later treatment of symptomatic HIV infection: Report of the VA Cooperative study. Paper presented at the Institut Pasteur, Paris, France, March 5, 1993.

7. Hamilton JD. Implications of early versus later treatment of symptomatic HIV infection: Report of the VA Cooperative study. Paper presented at the Karolinska Institut, Stockholm, Sweden, March 8, 1993.

8. Hamilton JD. Clinical care and prevention insights from early intervention research. Presentation to be made at the AMA Early Intervention Conference, which precedes the IX International Conference on AIDS, Berlin, Germany, June 6, 1993.

Table 1

SUMMARY OF CLINICAL OUTCOMES - PROGRESSION TO AIDS

	Early N (%)	Late N (%)	P value	Relative Risk (L/E)	95% Confidence Interval
Number of Patients	170	168			
Overall	50 (29)	68 (40)	0.07	1.96	(1.00 ... 3.08)
Low Stratum	19 (41)	24 (53)	0.23		
High Stratum	31 (25)	44 (36)	0.14		
White	29 (27)	51 (46)	0.007	1.92	(1.22 ... 3.04)
Low	11 (32)	19 (59)	0.02		
High	18 (25)	32 (41)	0.07		
Black/Hispanic	21 (33)	17 (30)	0.45	0.78	(0.41 ... 1.44)
Low	8 (67)	5 (38)	0.11		
High	13 (25)	12 (27)	0.93		
Non-IVDU	36 (28)	55 (42)	0.03	1.58	(1.04 ... 2.41)
Low	12 (35)	20 (56)	0.08		
High	24 (26)	35 (39)	0.14		
IVDU	14 (32)	13 (34)	0.92	1.05	(0.49 ... 2.24)
Low	7 (58)	4 (44)	0.62		
High	7 (23)	9 (31)	0.68		
Anergic	26 (46)	40 (58)	0.23	1.36	(0.82 ... [illegible])
Reactive	24 (21)	28 (28)	0.36	1.29	(0.[illegible] ... [illegible])

PROGRESSIONS

	First diagnosis		Subsequent diagnoses	
	Early	Later	Early	Later
PCP	17	19	13	[illegible]
Esophageal Candidiasis	12	9	8	[illegible]
MAI	3	3	10	[illegible]
Toxoplasmosis	1	2	0	
Cryptosporidiosis	0	1	0	[illegible]
PML	0	2	0	[illegible]
CMV	2	5	5	[illegible]
Disseminated Simplex	1	1	[illegible]	[illegible]
Disseminated TB	1	0	2	[illegible]
Dementia	0	7	2	[illegible]
Wasting	2	9	0	[illegible]
KS	6	5	10	[illegible]
Visceral KS	0	0	[illegible]	[illegible]
Lymphoma	1	6	2	[illegible]
Total	46	65	58	[illegible]
Number of patients	46	65	28	[illegible]
Mean per patient	1	1	2.1	[illegible]
Percent with later diagnosis			61	[illegible]

Table 3

SUMMARY OF CLINICAL OUTCOMES - TIME TO DEATH

	Early N (%)	Late N (%)	P value	Relative Risk (L/E)	95% Confidence Interval
Number of Patients	170	168			
Overall	53 (31)	57 (34)	0.97	1.06	(0.73 1.54)
Low Stratum	19 (41)	20 (36)	0.86		
High Stratum	34 (27)	37 (18)	0.97		
White	32 (30)	47 (42)	0.20	1.47	(0.93 2.30)
Low	13 (38)	16 (50)	0.41		
High	19 (26)	31 (39)	0.25		
Black/Hispanic	21 (33)	10 (18)	0.05	0.44	(0.21 0.93)
Low	6 (50)	4 (31)	0.19		
High	15 (29)	6 (14)	0.04		
Non-IVDU	41 (32)	47 (36)	0.69	1.09	(0.73 1.64)
Low	13 (38)	17 (47)	0.52		
High	28 (30)	30 (32)	0.91		
IVDU	12 (28)	10 (26)	0.37	0.91	(0.39 2.11)
Low	6 (50)	3 (33)	0.30		
High	6 (19)	7 (24)	0.75		
Time to AIDS or Death					
Overall	66 (39)	71 (42)	0.47	1.14	(.78 1.66)

TABLE 4

RELATIVE RISK OF PROGRESSION TO AIDS OR DEATH BY BASELINE PARAMETERS*

	UNIVARIATE ANALYSES			MULTIVARIATE ANALYSES		
	Relative Risk	95% CI	P-value	Relative Risk	95% CI	P-value
PROGRESSION TO AIDS						
Age > 40	1.77	(1.16, 2.80)	0.013	1.67	(1.02, 2.73)	0.042
CD4 < 350	1.73	(1.07, 2.80)	0.022	1.27	(0.76, 2.10)	0.36
p24 positive	2.44	(1.44, 4.14)	<0.001	2.23	(1.27, 3.92)	0.006
β_2 > 4	2.23	(1.36, 3.65)	0.001	2.12	(1.30, 3.46)	0.003
Anergie	2.28	(1.43, 3.61)	<0.001	2.00	(1.24, 3.26)	0.005
Delayed treatment				1.66	(1.01, 2.70)	0.047
DEATH						
Age > 40	2.85	(1.31, 4.63)	0.004	1.53	(0.79, 2.97)	0.21
CD4 < 350	3.46	(1.63, 7.32)	0.001	2.70	(1.27, 5.76)	0.010
p24 positive	2.39	(1.16, 4.90)	0.016	2.55	(1.18, 5.47)	0.017
β_2 > 4	2.04	(1.04, 4.00)	0.034	2.07	(1.07, 4.00)	0.030
Anergie	1.96	(1.06, 3.62)	0.028	1.89	(0.98, 3.62)	0.056
Delayed treatment				0.84	(0.44, 1.60)	0.59

*Calculated using Cox regressions

Figure 1

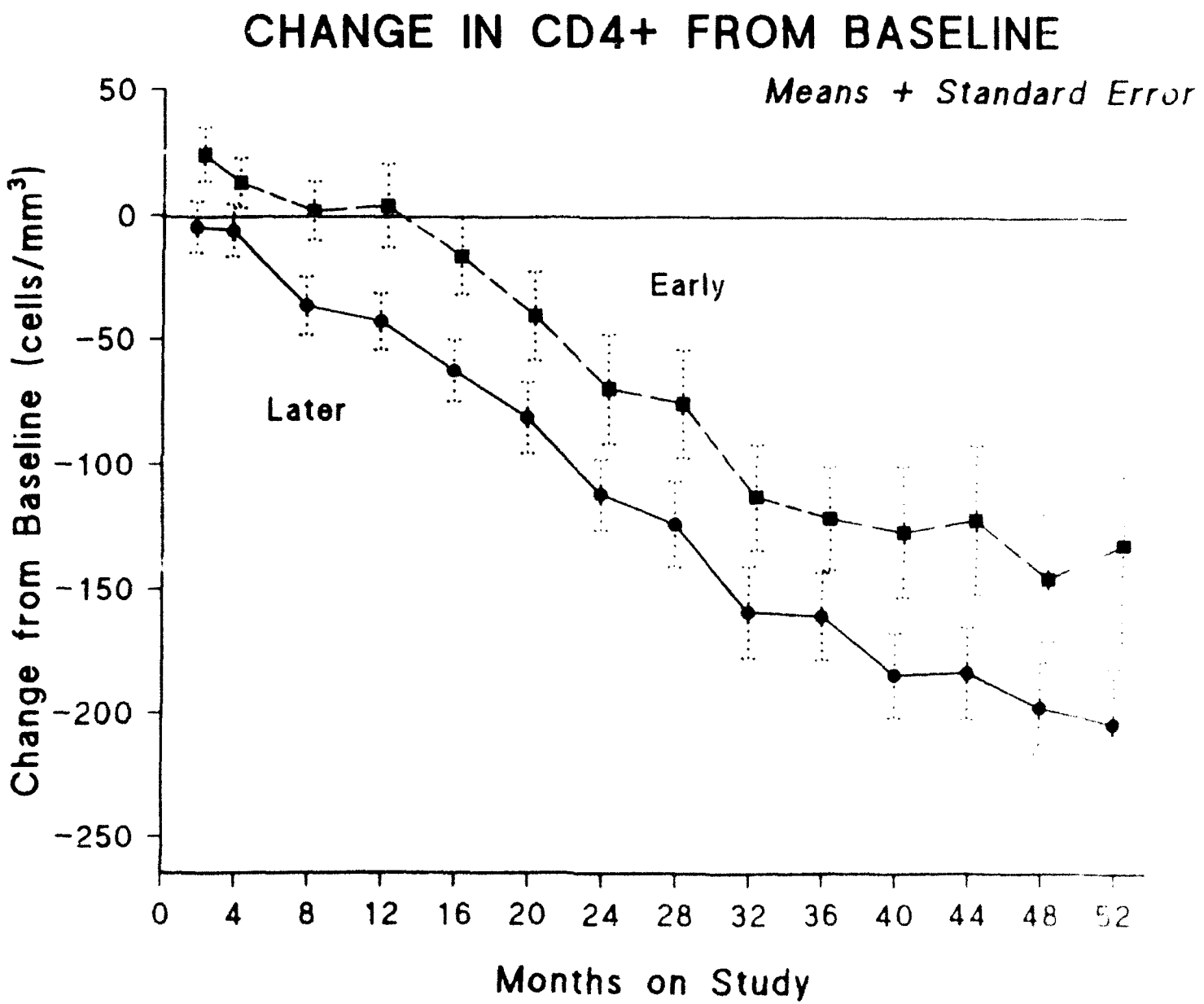

CHANGE IN CD4+ FROM BASELINE
Means + Standard Error
Change from Baseline (cells/mm³)
50
0
-50
-100
-150
-200
-250
Early
Later
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Months on Study

Figure 2

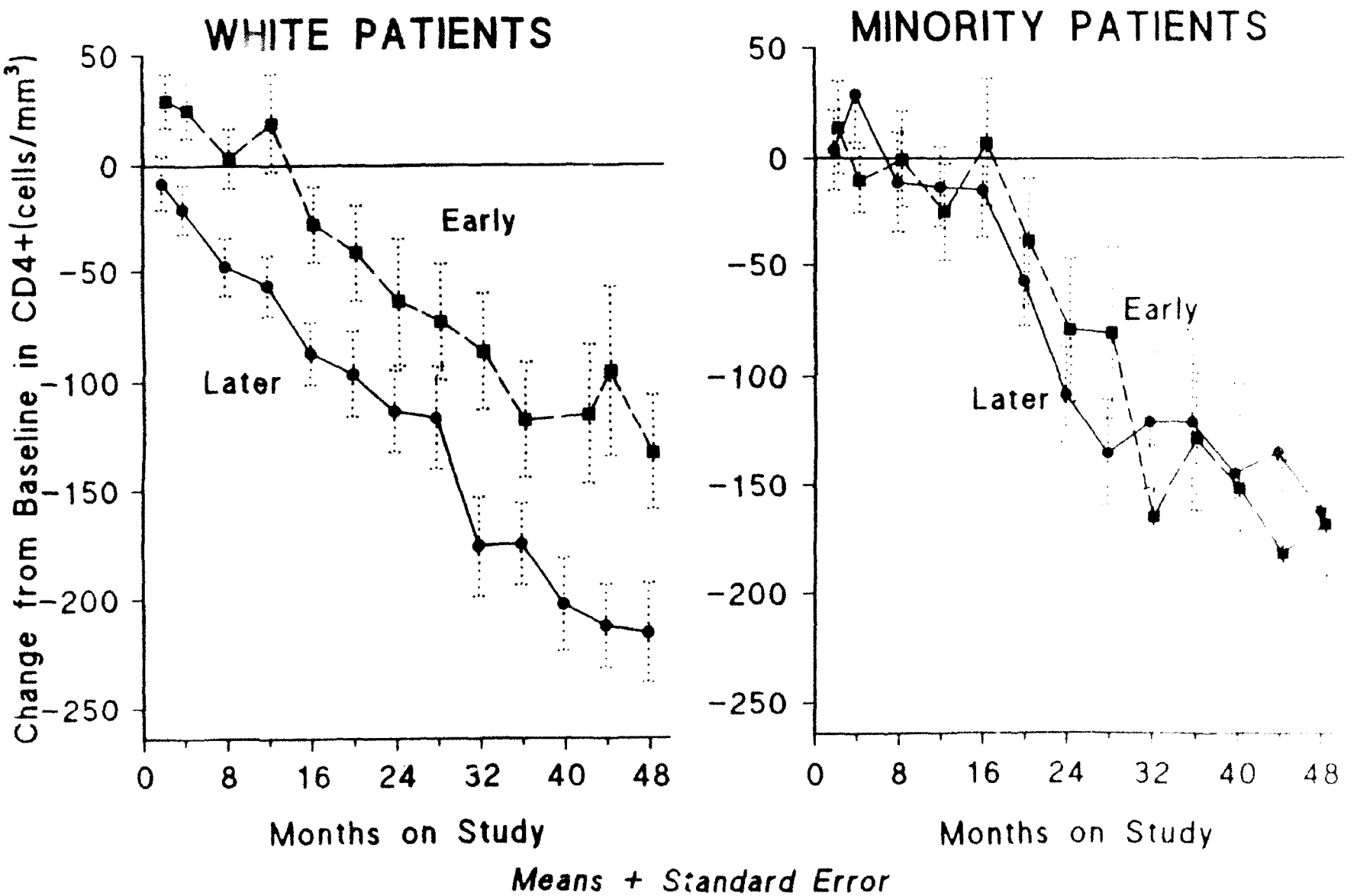

WHITE PATIENTS
MINORITY PATIENTS
Change from Baseline in CD4+(cells/mm³)
50
0
-50
-100
-150
-200
-250
Early
Later
0
8
16
24
32
40
48
Months on Study
Means + Standard Error

Figure 3

SURVIVAL AFTER AN AIDS DIAGNOSIS

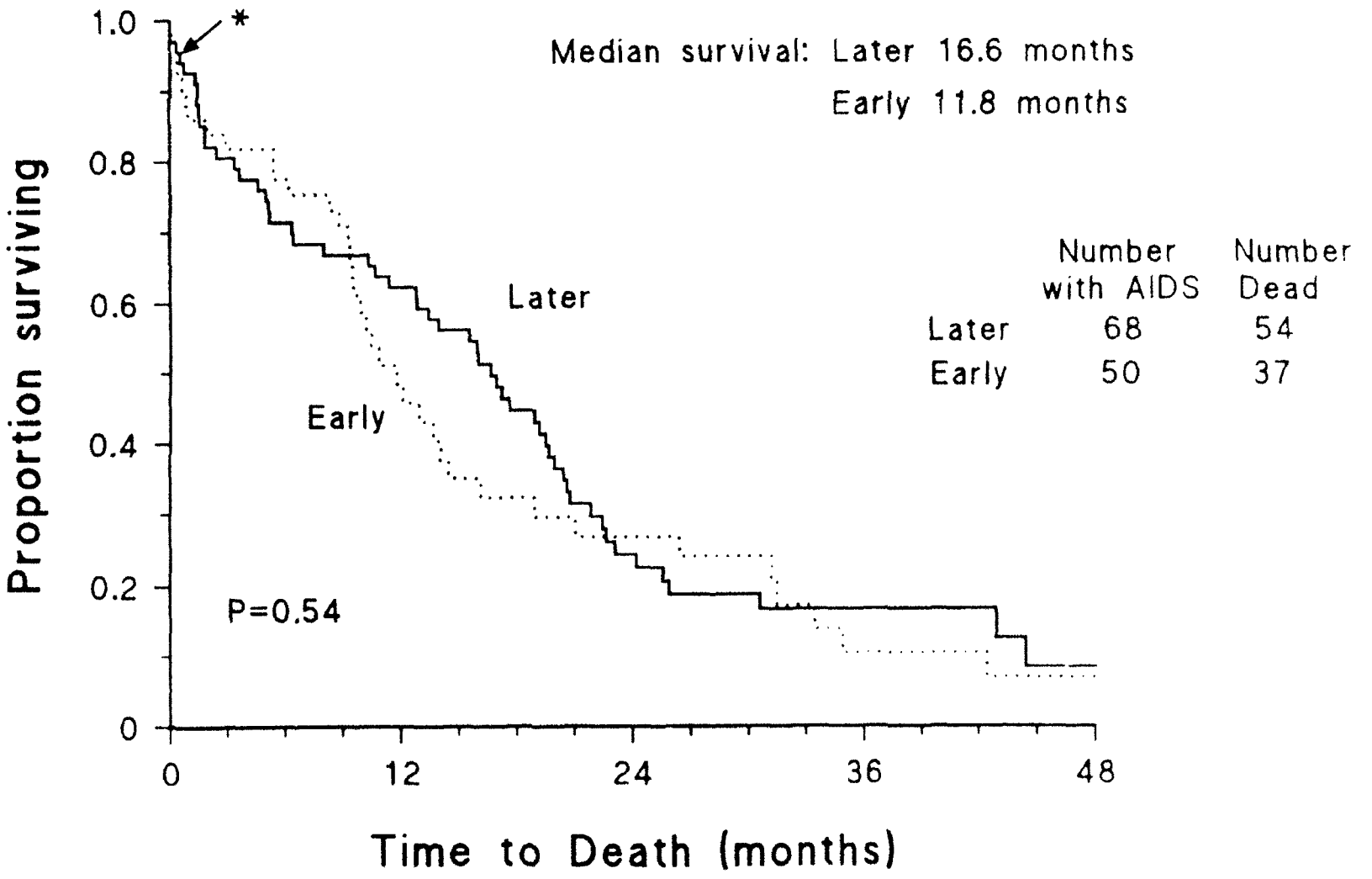
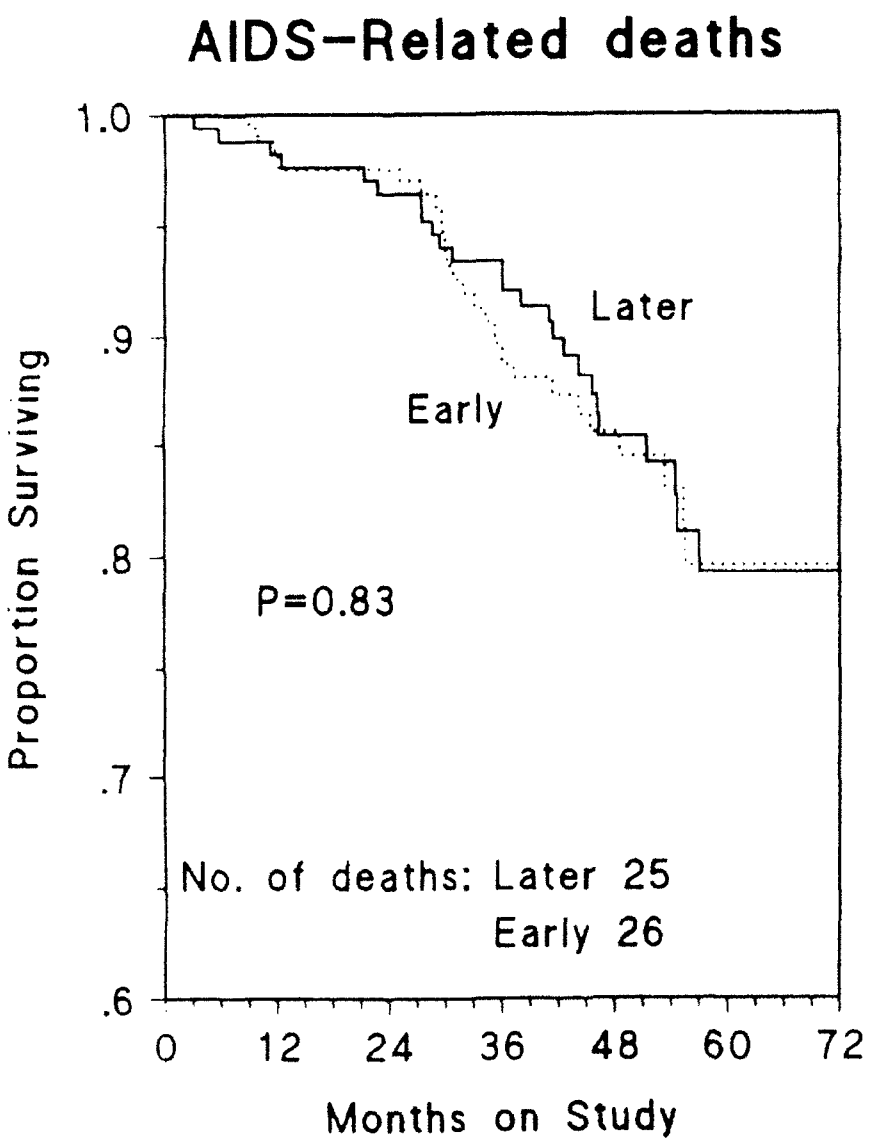
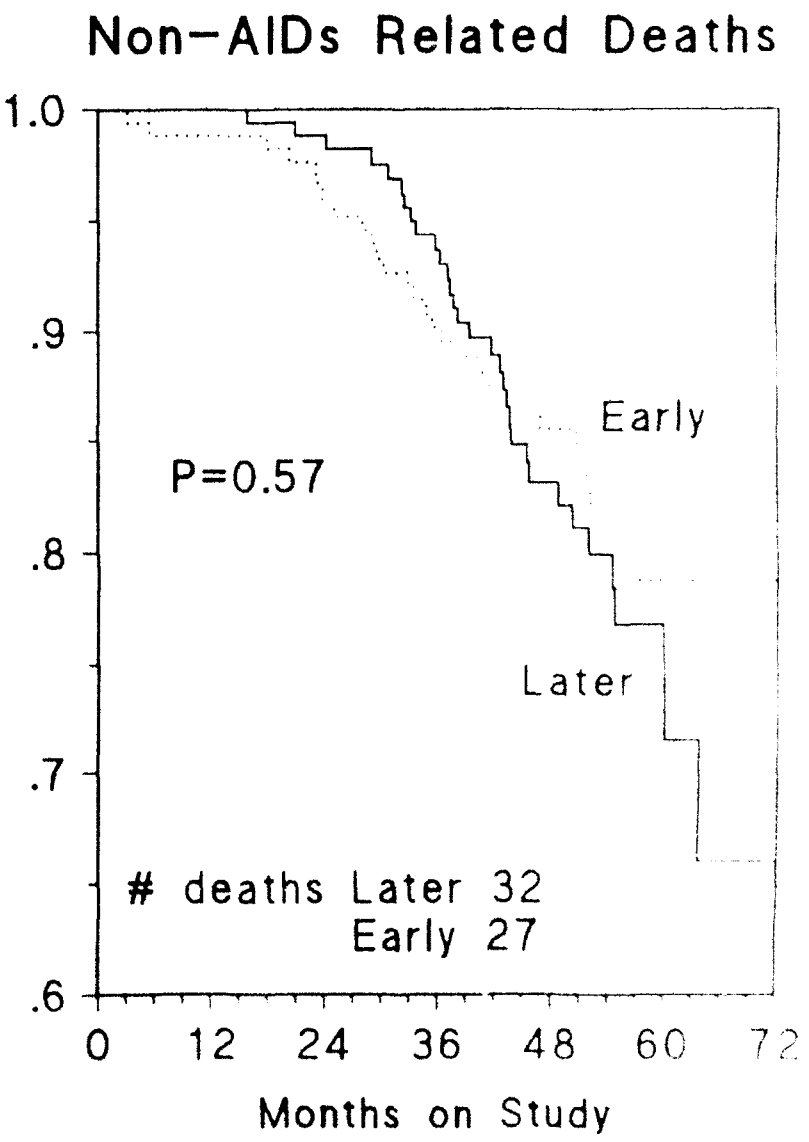


Figure 4


AIDS-Related deaths
1.0
.9
.8
.7
.6
Proportion Surviving
Later
Early
P=0.83
No. of deaths: Later 25
Early 26
0
12
24
36
48
60
72
Months on Study


Non-AIDs Related Deaths
1.0
.9
.8
.7
.6
Early
P=0.57
Later
deaths Later 32
Early 27
0
12
24
36
48
60
72
Months on Study